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Tremor and Other Hyperkinetic Movements

Case report

Neurodegeneration with Brain Iron Accumulation: Two Additional Cases with Dystonic Opisthotonus

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Abstract

Background: Specific phenomenology and pattern of involvement in movement disorders point toward a probable clinical diagnosis. For example, forehead chorea usually suggests Huntington's disease; feeding dystonia suggests neuroacanthocytosis and risus sardonicus is commonly seen in Wilson's disease. Dystonic opisthotonus has been described as a characteristic feature of neurodegeneration with brain iron accumulation (NBIA) related to PANK2 and PLA2G6 mutations.

Case report: We describe two additional patients in their 30s with severe extensor truncal dystonia causing opisthotonic posturing in whom evaluation revealed the diagnosis of NBIA confirmed by genetic testing.

Discussion: Dystonic opisthotonus may be more common in NBIA than it is reported and its presence especially in a young patient should alert the neurologists to a possibility of probable NBIA.

Keywords: Opisthotonus, dystonia, neurodegeneration with brain iron accumulation, secondary, phenomenology, genetics, botulinum toxin

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Introduction

Phenomenology or pattern of movement helps in approaching and narrowing the differential diagnosis in a patient with movement disorder. For example, forehead chorea usually suggests Huntington's disease; feeding dystonia is characteristically seen in neuroacanthocytosis.[1,2] Similarly, oromandibular dystonia is usually seen in neuroleptic-induced tardive dystonias, neuroacanthocytosis, Wilson's disease, and Lesch–Nyhan syndrome.[3–6] Neurodegeneration with brain iron accumulation (NBIA) is a group of progressive neurodegenerative disorders characterized by extrapyramidal involvement and evidence of iron accumulation in the brain.[7] Pantothenate kinase-associated neurodegeneration (PANK) accounts for 50% cases of NBIA.[7] Dystonic opisthotonus as a manifestation of NBIA was first described by Ludo Von Bogaert in 1936.[8] Stamelou et al. reported that four of eight patients of theirs with NBIA had opisthotonus and all of these had either PANK2 or PLA2G6 mutations.[9] We report two additional patients, both in their 30s, who presented with action-induced dystonic opisthotonus and clinical exome sequencing clinched the diagnosis of NBIA.

Case Reports

Case 1

A 34-year-old male presented with 3-year history of severe arching of the back with involuntary closure of eyes. Examination revealed severe dystonic opisthotonus and blepharospasm (Video: Segment 1). There was no history of exposure to neuroleptic drugs prior to the occurrence of movement disorder. He had a negative family history with normal ceruloplasmin levels. Nerve conduction studies showed sensorimotor neuropathy. Magnetic resonance imaging (MRI) brain revealed iron deposition in bilateral globus pallidus on T2-weighted and Susceptibility-weighted images (SWI) producing

Segment 1: Severe Extensor Truncal Dystonia and Blepharospasm.

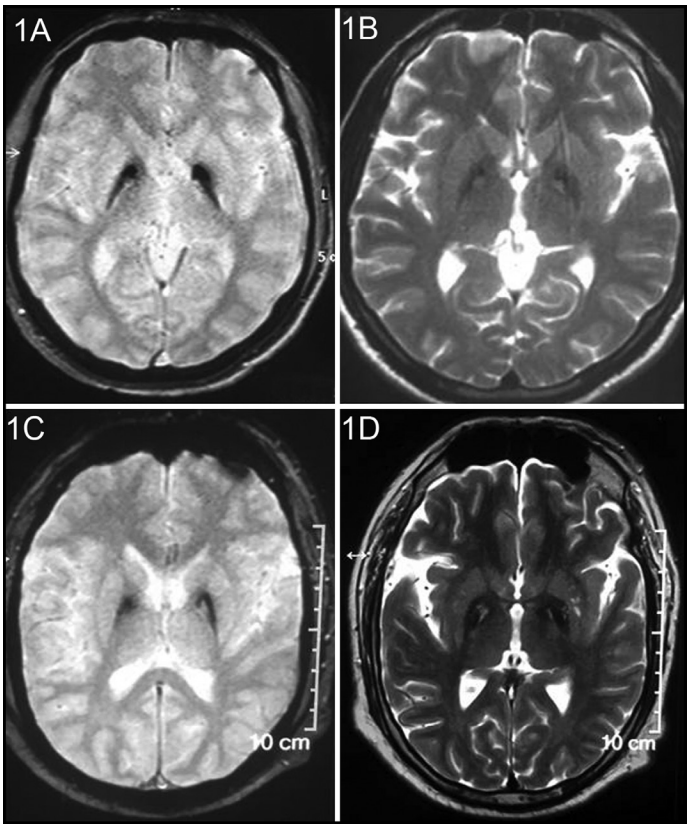

Figure 1. **Magnetic Resonance Imaging of the brain.** (A–D) MRI Brain Showing Iron Deposition in Bilateral Globus Pallidus on SWI and T2W Images Depicting "Eye of the Tiger Sign."

Segment 2: Demonstration of Severe Extensor Truncal Dystonia with Spread to the Upper Limbs and Lower Face with Partial Response to Botulinum Toxin.

the classical "eye of the tiger sign" (Figure 1A,B). Genetic analysis revealed a pathogenic variant (c.545_546 ins A (p. R183fs*47) in Exon 1 of PANK 2 gene. Another variant of unknown significance (compound heterozygous variant: c.1063 A>G (p.K355E) in Exon 3 of PANK2 gene was also detected. He did not show a good response to a combination of drugs (trihexiphenidyl 12 mg/day, tetrabenazine 75 mg/day, and baclofen 60 mg/day) and botulinum toxin therapy (500 units of abobotulinum toxin injections into the paraspinal muscles and orbicularis oculi).

Case 2

A 33-year-old male presented with abnormal posturing of left upper limb and arching of the back for the past 5 years. Family history was noncontributory. There was no history of exposure to neuroleptic drugs prior to the occurrence of movement disorder. Examination revealed severe extensor truncal dystonia with spread to upper limbs and face (Video: Segment 2). Examination was negative for any ocular, pyramidal, cranial nerve, or cognitive

involvement. On evaluation, T2 hypointense lesions with central hyperintensity in bilateral globus pallidus (eye of the tiger sign) were found on MRI brain (Figure 1C,D). Genetic analysis revealed a compound heterozygous mutation c.434C>A (p.S145) pathogenic variant and c.1432 A>G (p.K478E) variant of uncertain significance in the PANK 2 gene. He showed a modest subjective response of 30% with a combination of oral drugs (trihexiphenidyl 30 mg/day, levodopa 400 mg/day, and clonazepam 6 mg/day) and periodic botulinum toxin therapy (600 units of abobotulinum toxin into paraspinal muscles per session). He was able to walk erect with this combination of drugs and botulinum toxin injections every 3 months as demonstrated in the video.

Discussion

We describe two patients who presented with severe extensor truncal dystonia and genetic testing clinched the diagnosis of NBIA. Dystonic opisthotonus commonly occurs in secondary dystonias, while it is highly uncommon in primary dystonias. Differential diagnosis usually includes exposure to antipsychotic drugs, neurometabolic disorders (Wilson's disease, Lesch–Nyhan syndrome, and maple syrup urine disease), and NBIA.[9,10] There are certain clues from history, examination, or MRI brain imaging which can help in narrowing the differential diagnosis in a patient who presents with severe arching of the back and neck. A history of neuroleptic exposure would point towards a tardive etiology. Inborn errors of metabolism like maple syrup urine disease or glutaric aciduria usually have a very early age of onset, delayed motor milestones with presence of fever exacerbating dystonic crisis and encephalopathy. Wilson's disease can be excluded by slit lamp examination for Kayser–Fleischer rings and copper studies. Rarely, dopa-responsive dystonia can also present with dystonic opisthotonus. Genetic testing is not always possible in such a scenario, especially in a low socioeconomic setting. Clinical clues may help in recognizing such intricate and complex movement disorders.

To conclude, dystonic opisthotonus may be more commonly seen in NBIA than it is reported, and its presence should alert the neurologists to a possibility of probable NBIA.

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